

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/EP2022/062480	International filing date (day/month/year) 09.05.2022	Priority date (day/month/year) 12.05.2021
International Patent Classification (IPC) or both national classification and IPC INV. A61P35/00 A61P1/00 A61P9/00 A61P11/00 A61P21/00 A61P25/16 A61P27/02 A61P29/00 C07D491/048 C07D491/107 C07D498/04 C07D498/10 A61K31/519 A61K31/5386 A61K31/444 C07D213/74 C07D401/04		
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Bedel, Christian Telephone No. +49 89 2399-0
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-19, 21-33</u>
	No: Claims	<u>20</u>
Inventive step (IS)	Yes: Claims	<u>1-19, 21-33</u>
	No: Claims	<u>20</u>
Industrial applicability (IA)	Yes: Claims	<u>1-33</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

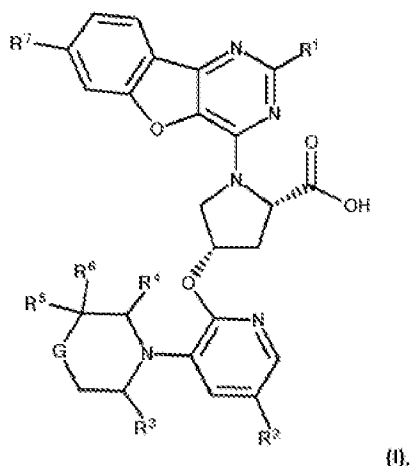
see separate sheet

Re Item V

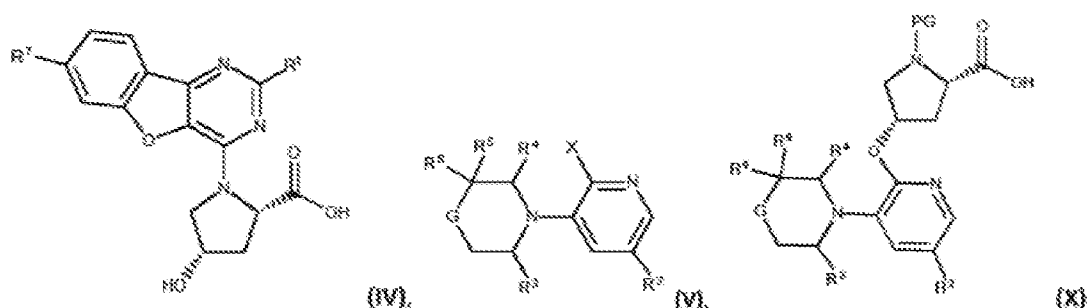
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Application

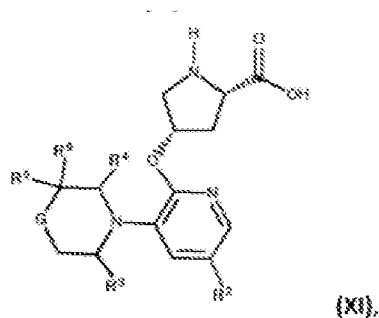
1.1 Claim 1 concerns a compound of formula (I):



1.2 Claim 20 concerns intermediate compounds of formula (IV), (V), (X) and (XI) as follows:

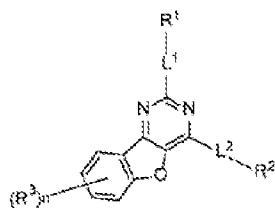


and

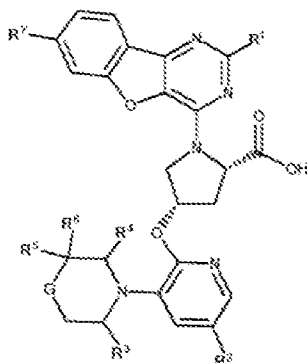


1.3 Claim 21 further concerns a esterified prodrug derivatives (A) and (A') of compound (I).

- 1.4 Claims 23-33 concern therapeutical application claims based on the inhibition of cGAS.
- 2 Prior art
- 2.1 Reference is made to the following documents:
- D1 WO 2006/047504 A1 (JANSSEN PHARMACEUTICA NV [BE]; ILLIG CARL R [US] ET AL.) 4 May 2006 (2006-05-04)
 - D2 WO 2010/057126 A1 (AMGEN INC [US]; ALLEN JENNIFER R [US] ET AL.) 20 May 2010 (2010-05-20)
 - D3 WO 2011/092272 A1 (HOFFMANN LA ROCHE [CH]; BAUMANN KARLHEINZ [DE] ET AL.) 4 August 2011 (2011-08-04)
 - D4 WO 2016/038581 A1 (NOVARTIS AG [CH]; BURGER MATTHEW T [US] ET AL.) 17 March 2016 (2016-03-17)
 - D5 WO 2020/142729 A1 (BELLBROOK LABS [US]) 9 July 2020 (2020-07-09) cited in the application
- 3 Novelty (Art. 33(2) PCT)
- 3.1 D1-D4 discloses compounds that fall within the scope of claim 20 and formula (V) (see references in search report). Claim 20 is consequently not novel.
- 3.2 The compounds of formula (I) of claim 1 and of formula (A) and (A') of claim 21 do not appear to be disclosed in the prior art and are consequently novel. The same holds true for the corresponding dependent claims as well as for the application claims 23-33.
- 4 Inventive step (Art.33(3) PCT)
- 4.1 D1-D4 are relevant only for the intermediate compounds of formula (V) and relate to a completely different field.
- 4.2 The closest prior art can be regarded as D5 which also discloses cGAS inhibitors of the formula:



The presently claimed compounds of formula (I)



vis à vis the general formula of D5 on account of the piperidine/piperazine/morpholine group directly linked to the pyridine ring. This possibility is not encompassed by D5 so that the present scope does not overlap with the one of D5.

- 4.3 It appears that the compounds of the invention have a better cGAS inhibition activity compared to the ones of D5 (compare table 1 and comparative examples taken from D5 in table 2).
- 4.4 The technical problem can therefore be regarded as the provision of better cGAS inhibitors and medicaments for use in the treatment of diseases caused by an over activity of said cGAS.
- 4.5 The present compounds appear to be a credible solution to this problem firstly in view of the numerous examples and comparative examples provided and secondly because it appears likely that cGAS inhibition may have a positive effect for in particular inflammation diseases (see discussion of the prior art related to cGAS pathway).
- 4.6 This solution is considered as inventive for the following reasons:

Given the structural differences between the compounds of D5 and the presently claimed compounds and the proven enhanced inhibition effect, it cannot be said with any degree of accuracy that the skilled person, faced with the problem of providing enhanced cGAS inhibitors, would have been unambiguously led to prepare the compounds of the present application. Hence the present application as defined in claim 1 involves an inventive step.

- 4.7 As regard the prodrugs of claim 21, which are the esterified version of the present carboxylic acid derivatives of claim 1, as can be seen in table 3, they show a clear decreased inhibition effect in vitro compared to the corresponding active drug. It is therefore very likely that they become active again with a delayed effect in the body fluids of the patient to be treated. Therefore an inventive step could be acknowledged.
- 4.8 As regard the intermediates of claim 20, although the latter is not novel, the documents D1-D4 relevant to novelty concern only the intermediate of formula (V). The other intermediates (IV), (X) and (XI) appear to be novel and could be considered inventive as "key intermediates" in so far as they provide the structural part that make a contribution over the prior art D5. Regarding intermediate (IV), it is noted that none of the examples of D5 discloses an ether linkage between the pyrrolidine and a pyridine ring, therefore said hydroxy-pyrrolidine intermediate of formula (IV) could also be considered as inventive as "key intermediate".

Re Item VIII

Certain observations on the international application

- 1 Clarity (Art. 6 PCT)
- 1.1 The use of the term "prodrug" in claims 1-19 is unclear because it defines a compound structure with a functional feature and therefore potentially covers an undefined amount of compounds, contrary to the requirements of Article 6 PCT. Likewise the term "prodrug" should be avoided in the description unless it directly refers to precisely defined chemical groups (like in the subject-matter of claim 21).
- 1.2 Second medical use claim 23 is not acceptable under Article 6 PCT. The therapeutic application is functionally defined by a mechanism of action which does not allow practical application in the form of a defined, real treatment of a pathological condition (disease) (G-II, 4.2).
- The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional condition(s) would fall within the functional definition (C-III, 6.5).

- 1.3 Particular attention should be paid to vague expression like "and the like", "etc..." or to any passage of the description that tends to extend the scope of the application beyond what is strictly delimited by the claims. These passages or expressions should be either deleted or amended.
- 1.4 Likewise such expression as "incorporated by reference" that follows the citations of any prior art should be deleted.